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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RISHI, ANJUM I	

ART UNIT	PAPER NUMBER
1632	5

DATE MAILED: 12/28/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/654,276	Applicant(s) COHEN ET AL.	
	Examiner Anjum Rishi	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of repairing a damaged myocardium in a mammal comprising: 1) providing a three dimentional porous polysaccharide matrix; wherein matrix comprise controlled release polymeric microspheres containing growth factors 2) introducing fetal cardiomyocytes or autologous myocytes into the matrix and forming a tissue-engineered biograft *in vitro; and 3)* further transplanting the biograft onto myocardial tissue of a mammal, does not reasonably provide enablement for repairing a damaged myocardium in a mammal by introducing any cell types into the matrix to form a biograft and transplanting it onto the myocardium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are directed to a method for repairing a damaged myocardium in a mammal by providing a three-dimentional polysaccharide matrix, wherein mammalian cells are grown *in vitro*, to form a tissue engineered biograft. Further implanting the tissue engineered biograft onto the myocardial tissue of a mammal, wherein the polysacchride matrix is an alginate which generates a scaffold and comprise controlled release polymeric microspheres which release growth factors, genes or DNA. Further

the cardiomyocytes are co-cultured with endothelial cells, fibroblasts or smooth muscle cells, wherein the endothelial cells form capillary-like tubes within the scaffold. Further the myocardial damage is due to infarction or congenital heart disease.

The teachings of the working examples demonstrate the preparation of a scaffold using fetal cardiomyocytes of rat by culturing the cardiomyocytes in an alginate scaffold. The specification concludes that the cells were viable and contracting as seen by electron microscope. Further, microspheres containing soluble factors i.e. growth factors, were added to the scaffold and biograft was transplanted in experimental rats in which myocardial infarction was induced. The specification concludes from their data that neovascularization and myofibre formation occurs in implanted biograft nine weeks post-implant. Specification results suggests presence of mechanical and electrical connections among the cardiomyocytes. Further echo done on the control and treated rats to evaluate contractility, suggested typical heart failure following myocardial infarction in controls, while treated rats showed no dilatation which suggested no heart failure. Specification concludes from their results that treated rats did not have heart failure.

The working examples are not sufficient to support the breath of the claims, wherein the claims encompasses efficacy of the instantly claimed invention in a mammal by using any and all cell types. Cardiomyocytes are different from other cell types due to their inherent property of spontaneous contractility and rapid spread of cardiac impulse. The specification does not teach which other types of cells possess these same properties. Further, the specification doesn't provide sufficient guidance that

cells that lack these properties would be capable of treating heart failure or heart disease in general. The working examples also disclose microspheres releasing soluble growth factors only. The specification does not provide any guidance as to the type, mechanism or level of soluble factors released by the microspheres as claimed i.e. genes, DNA (no-gene), and growth factors which correlates with any therapeutic effect in myocardial disease.

In addition, the specification does not address the issue of transplant rejection and graft-versus host disease which is well known in the art. "The use of viable cellular grafts in humans would require either the long-term administration of immunosuppressants or the use of nonantigenic cells. Obtaining an adequate number of nonantigenic or syngeneic cells of the appropriate cell type may be difficult." (Li et al, (1999), Circulation, vol. 19, pages :1163-1169 ; See page 1169, second paragraph). The specification reads on the installation of xenogeneic or allogeneic cells into a mammal. In the absence of substantial immunodeficiency, foreign tissue is rapidly rejected by the host mammal's immune system. Rejection is largely mediated by complement, cytotoxic T cells, and antibody-dependent cellular cytotoxicity. Antibody mediated rejection of tissue is particularly strong in the case of discordant xenogeneic tissue due to the presence of preformed anti-xenogeneic antibodies in the host mammal. Xenogeneic transplantation can be sub-divided into two categories, concordant and discordant, depending on the degree of genetic disparity between the donor and host species. Whereas transplantation between a rat and a mouse is considered concordant, transplantation between a mouse and a human, or a pig and a

human is considered discordant. The host immune response to a discordant graft is significantly stronger than that observed to a concordant graft due primarily to the increased frequency of natural preformed antibodies in the host that recognize discordant antigens and cause hyperacute rejection of the foreign tissue. Naturally occurring xenoantibodies can mediate hyperacute rejection (HAR) of xenogeneic tissue in as little as 2 hours (Kaufman et al., (1995), Annu. Rev. Immunol., Vol. 13, 339-367). Prevention of rejection in xenotransplants requires inhibition or suppression of multiple components of both the immune and inflammatory responses. According to Kaufman et al., " In experimental and clinical protocols in which immunosuppressive agents ... were administered to recipients of xenografts, vigorous rejection occurred , even when profoundly immunosuppressive combinations of agents were utilized, " (Kaufman et al. (1995), *supra*, page 347). The specification does not identify an immunosuppressive agent or combination of agents capable of rendering a recipient animal tolerant to xenogeneic or allogeneic tissue or provide sufficient guidance as to the level of immunodeficiency necessary to allow xenogeneic or allogenic cells to form a graft without activating the immune system. Further, the specification does not disclose how to overcome the issue of appropriate sizing of the graft which is correlated with any improvement in myocardial function using any type of cells. Another issue which the specification does not address is the prevention of activation of coagulation system which leads to graft thrombosis or embolic complications. (See Li et al,page 1169, column 1, first paragraph).

Thus the specification is only enabling for the treatment of a damaged myocardium by transplanting a biograft using fetal cardiomyocytes or autologous cardiomyocytes. The specification does not provide sufficient guidance for the use of other cell types that would treat cardiac damage without activating graft rejection. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves., see In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Thus, due to the art recognized unpredictability of preventing graft rejection in allografts and xenografts, obtaining appropriate number of nonantigenic or syngeneic cells of the appropriate cell type, and the lack of guidance provided by the specification in using any cell type, selecting the appropriate graft size and preventing thrombo-embolism, lack of type and level of soluble factors released by the microspheres, and the breadth of the claims, it would have required undue experimentation to practice the scope of instant invention and the skilled artisan would not have predicted success in repairing a damaged myocardium in any mammal by providing a polysaccharide matrix; introducing any mammalian cell types into the matrix; forming a tissue engineered biograft *invitro* ; and transplanting the graft onto the myocardial tissue.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-15 provides for the use of a porous polysaccharide matrix, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 11-15 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11-17 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by PCT number WO 97/44070 published 11/27/97, hereafter refered to as Shapiro et al.

In regards to the intended use of a polysaccharide matrix for the transplantation of mammalian cells into the heart, it is noted that the use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim

does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

The claims are directed to a porous polysaccharide matrix comprising a three-dimensional tissue engineered biograft , wherein the polysaccharide is an alginate polysaccharide containing mammalian cells which have been cultured in the matrix *in vitro*.

Shapiro et al teaches an alginate polysaccharide matrix comprising a three-dimentional tissue engineered biograft, wherein mammalian cells including fibroblasts and artificial organ equivalent cells representative of the organ have been cultured in the matrix *in vitro*. (See Shapiro et al, page1, line 1-15, page 2, line 7, page 4, line 9, page 8, line 22-23, page17, line 6-11)

Thus by teaching the all the elements of the claims, Shapiro et al. anticipates the instant invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4, 9 and 11-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Leor et al, (Leor et al, (1999), European heart journal, vol. 20, page 29)

This reference qualifies as prior art since the inventorship is different, i.e. not all authors of the Leor et al. reference are listed as inventors on the instant application.

The claims are drawn to a method of repairing a damaged myocardium in a mammal by providing a three dimentional polysaccharide matrix which generates a scaffold; introducing mammalian cells into the matrix *invitro* until a tissue engineered biograft is formed; transplanting the biograft onto the myocardial tissue of a mammal, wherein the polysaccharide matrix is an alginate matrix and generates a scaffold, wherein myocardial damage is due to myocardial infarction.

Leor et al teaches a method of repairing a damaged myocardium in a mammal by providing a three dimentional polysaccharide matrix which generates a scaffold; introducing mammalian cells into the matrix *invitro* until a tissue engineered biograft is formed; transplanting the biograft onto the myocardial tissue of a mammal, wherein the polysaccharide matrix is an alginate matrix and generates a scaffold, wherein myocardial damage is due to myocardial infarction. (See page 29, abstract 340).

Thus by teaching the all the elements of the claims, Leor et al anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 3, 4, 7, and 8, are rejected under 35 U.S.C. 103(a) as being unpatentable over US patent number 6,099,832, published 08/08/2000, hereafter refered to as Mickle et al, in view of PCT number WO 99/03973, published 1/28/99, hereafter refered to as Osiris therapeutics, and PCT number WO 97/44070, published 11/27/97, hereafter refered to as Shapiro et al, and US patent number 5,494,682, published 2/27/96, hereafter refered to as Cohen et al.

The claims are drawn to a method of repairing a damaged myocardium in a mammal by providing a three dimentional polysaccharide matrix which generates a scaffold; introducing mammalian cells into the matrix *in vitro* until a tissue engineered biograft is formed; wherein mammalian cells are selected from the group consisting of fetal cardiomyocytes, neonatal cardiomyocytes, adult cardiac cells, fibroblasts, smooth muscle cells, endothelial cells skeletal myoblasts, mesenchymal and embryonic stem cells; transplanting the biograft onto the myocardial tissue of a mammal, wherein the polysaccharide matrix is an alginate matrix and generates a scaffold and further comprise controlled release polymeric microspheres which release soluble factors comprising growth factors, genes or DNA.

Mickle et al teaches method of repairing a damaged myocardium in a subject by transplantation of cells into scar tissue of damaged myocardium. Further he recites that

the mammalian cell can be from a group consisting of fetal cardiomyocytes,adult cardiomyocytes, fibroblasts, smooth muscle cells, endothelial cells, and skeletal myoblasts. He also teaches culturing of the cells prior to transplantation in a biodegradable scaffolding, and further discloses a mechanism for the delivery of genes using such transplant. (See Mickle et al, column 1, line 8-15 and column 3, line 18). Mickle differs from the present invention by not teaching polysaccharide or alginate matrix and polymeric microspheres which release growth factors or DNA and does not include stem cells in the group of cells selected.

Shapiro et al supplements Mickle et al by teaching a biodegradable polysaccharide matrix made from alginate. (See Shapiro et al, page 5, line 7-21). He further provides motivation for using alginate polysaccharide matrix "the unique properties of alginate, together with its biocompatibility, its relatively low cost and wide availability have made alginate an important polymer in medicinal and pharmaceutical application ".(Shapiro et al, page 4, line 17-21). He further teaches that the matrix has microspheres encapsulating therapeutic agents like growth factors. He further provides motivation for using the growth factors, " it is advantageous to encourage a more rapid growth of the cells within the implant. Such factors are usually too small to be effectively retained within the sponge and hence are introduced in the form of slow release or controlled- release microcapsules into the spongue to provide for their effectivity." (See page 11, lines 10, 15, and 16). Cohen et al further supplements Mickle et al by teaching encapsulating nuceic acids within the polymeric microparticles and further provides motivation for encapsulating the nucleic acid. "a number of different materials can be

incorporated into the polymeric materials ranging from molecules as small as hormones and proteins to living cells. Materials in solution or in suspension can be encapsulated, including nucleic acids".(Cohen et al, column 5, line 46-60). Osiris therapeutics further supplements Mickle by teaching the use of stem cells for implantation.(see page 2 line 14). They provide motivation for using stem cells, "Mesenchymal stem cells differentiate into cardiac muscle cells and integrate with the healthy tissue of the recipient to replace the function of the dead or damaged cells, thereby regenerating the cardiac muscle as a whole".

In view of the motivation provided by Shapiro et al for using alginate polysaccharide matrix, the motivation provided by Osiris therapeutics to use stem cells, and the motivation provided by Cohen and Shapiro for including microspheres in the matrix as discussed in detail above, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the method of repairing a damaged myocardium taught by Mickle et al. to include a polysaccharide alginate matrix, microspheres and stem cells; in order to grow mammalian cells in the matrix and transplant the matrix into a damaged myocardium with a reasonable expectation of success.

Conclusion

No claim of the instant application has been allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anjum I Rishi whose telephone number is (703)308-4422. The examiner can normally be reached on M-F(8:30am-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached on (703)305-6608. The fax phone numbers for the organization where this application or proceeding is assigned are (703)308-4242 for regular communications and (308)8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the art Unit patent analyst Pinkeney Kay whose telephone number is (703)305-3553.

Anjum Rishi

A.M.S. BECKERLEG
PATENT EXAMINER